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COMPLETE SPECIFICATION.

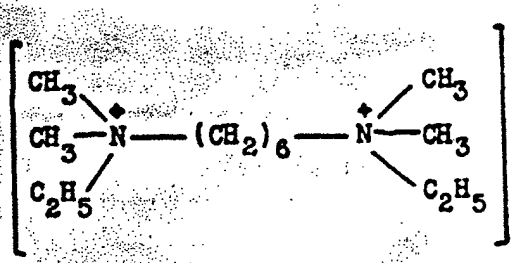
"New therapeutically active quaternary ammonium salts and processes for their preparation."

We, MAY & BAKER LIMITED, a British Company, of Dagenham, Essex, England, Manufacturing Chemists, hereby declare this invention and the manner in which it is to be performed, to be fully described and ascertained in and by the following statement:—

This invention relates to new quaternary ammonium compounds and to processes for their preparation.

It is well known that hexamethylene-1:6-bis-trimethyl-ammonium salts have useful therapeutic application as ganglionic blocking agents. It is the object of the present invention to provide new quaternary ammonium salts which have therapeutic advantage over these known salts.

The compounds of the present invention are the quaternary ammonium compounds which contain the cation represented by the formula:



In clinical trial, hexamethylene-1:6-bis-(ethyldimethyl-ammonium) dibromide, for example, was shown to be about four times as active as hexamethylene-1:6-bis-(trimethylammonium) dibromide in lowering the blood pressure in hypertensive patients. This result is quite unexpected since, for example, homologues in which the ethyl groups are replaced by n-propyl, isopropyl, n-butyl, isobutyl or allyl have been found to possess a wholly insignificant ganglionic blocking activity; moreover, the introduc-

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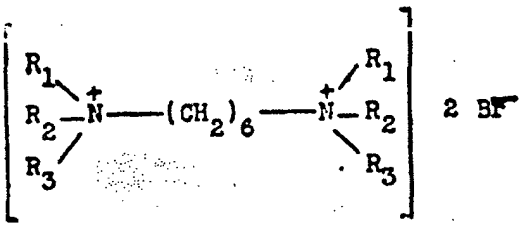
tion of more than two ethyl groups into the molecule likewise reduces ganglionic blocking activity.



These results are illustrated in the following table of biological data obtained with compounds of the type:

Compound tested			Relative Potency-paralysing ganglionic transmission	
R_1	R_2	R_3	Sympathetic ganglia (cat's superior cervical)	Parasympathetic ganglia (guinea pig's ileum)
CH_3	CH_3	CH_3	100	100
CH_3	CH_3	C_2H_5	150	200
CH_3	CH_3	n- C_3H_7	<5	<5
CH_3	CH_3	iso- C_3H_7	15	10
CH_3	CH_3	n- C_4H_9	<4	<2
CH_3	CH_3	iso- C_4H_9	<4	4
CH_3	CH_3	CH_2CH-CH_2	4	4
CH_3	C_2H_5	C_2H_5	75	100
C_2H_5	C_2H_5	C_2H_5	<5	<50

It will be appreciated that the nature of the anion of the salts of the present invention is not critical from the therapeutic standpoint; obviously anions which are pharmacologically undesirable should be avoided. Examples of suitable salts are the bromide, chloride, iodide, bitartrate, citrate and neutral sulphate.

The compounds of the present invention may be prepared by the application of any of the general methods heretofore employed for the production of bis-quaternary ammonium salts. However, in accordance with a feature of this invention, they are prepared either directly or through the intermediary of one or other of the following processes:

(a) the quaternation of hexamethylene-1:6-bis-(dimethylamine) using as quaternating agent a reactive ethyl ester such as ethyl bromide, chloride, iodide or sulphate.

(b) the quaternation of hexamethylene-1:6 - bis - (ethylmethylamine) using as quaternating agent a reactive methyl ester, or

(c) the condensation of a reactive diester of hexane 1:6-diol with dimethylethylamine.

These processes can be defined generically as residing in the interaction of a compound of the type:

$$X—(CH_2)_6—X$$

with a compound of the type Y in which, when X represents the acid residue of a reactive ester Y represents dimethylethylamine and, when X represents a dimethylamino or a methylethylamino radical Y represents a reactive ethyl or methyl ester. By the expression "a reactive ester" is meant esters known to be quaternising agents. In general such esters are the esters of strong acids, the acid residues of which may be, for example, halide, nitrate, sulphate and sulphonate.

It will be appreciated that salts which are not directly obtainable by means of the aforesaid processes, e.g., the tartrate or phosphate can be formed from the salts so obtainable either by direct methathesis or through the hydroxide as described heretofore in the chemical literature for the interconversion of quaternary ammonium salts. Water-soluble salts may also conveniently be produced by a further method which consists in treating an aqueous solution containing the required cation (and obtained by means of one of the aforesaid processes) with a water-soluble salt of 2:2-dihydroxy-1:1 - dinaphthyl - methane - 3:3-dicarboxylic acid (which acid—also called embonic acid—is practically insoluble in water even at boiling point), whereby the embonate containing the said cation is precipitated. This embonate will form an aqueous solution of reasonable concentration at elevated temperature and on treating a hot solution thereof with an acid corresponding to the required salt, embonic acid is precipitated leaving the required salt in solution in a substantially pure state.

The present invention is illustrated by the following Examples.

EXAMPLE I

A solution of ethyl bromide (436 g.) in ethyl alcohol (800 mls) is added slowly to a solution of hexamethylene-1:6-bis-dimethylamine (344 g.) in ethyl alcohol (1200 mls) which is being heated under reflux. The resulting solution is refluxed for a further 2 hours, then cooled in ice, the white solid which precipitates is filtered, washed with acetone and recrystallised from ethyl alcohol (800 mls).

Hexamethylene - 1:6 - bis - ethyldimethylammonium dibromide (429 g.) is obtained as a crystalline, slightly hygroscopic, white powder m.p. 258°C. (with decomposition).

Found	N	Br
	7.15	40.9
$C_{10}H_{34}N_2Br_2$ requires	7.2	41.0

EXAMPLE II

Embonic acid (41.5 g.) is dissolved in 2N sodium hydroxide solution (135 mls.) and, after dilution with water (428 mls.), the solution is heated to 60°C. Hexamethylene - 1:6 - bis - ethyldimethylammonium dibromide (41.8 g.) is dissolved in a mixture of water (135 mls.) and acetone (68,5 mls.) at 60°C. and the solution is added to the warm solution of sodium embonate. The clear solution obtained is cooled and the pale-brown solid precipitated is filtered off and recrystallised from a mixture of water and acetone to give hexamethylene - 1:6 - bis - (ethyldimethylammonium) embonate (61.6 g.) in the form of hydrated micro-needles, m.p. 262-265°C. (decomp.)

The embonate thus obtained is dissolved in hot water (1 litre) and to the boiling solution is added a solution of tartaric acid (30 g.) in water (200 mls.). After boiling for a further five minutes, the embonic acid precipitated is filtered off and washed three times with hot, distilled water. The combined filtrate and washings are evaporated on a steam bath and granulated with acetone. The crude product is recrystallised from methanol to give hexamethylene-1:6-bis - (ethyldimethylammonium) bitartrate (31 g.) as a white micro-crystalline powder, m.p. 169-170°C. (decomp.).

Having now fully described and ascertained our said invention and the manner in which it is to be performed, we declare that what we claim is:

1. A process for the production of quaternary ammonium salts, being hexamethylene - 1:6 - bis - (dimethylethylammonium) salts, which comprises reacting a compound of the type:

$$X—(CH_2)_6—X$$

with a compound Y in which X represents either the acid residue of a reactive ester or a dimethylamino or ethylmethylamino group and in which when X represents the acid residue of a reactive ester Y represents ethyldimethylamine and when X represents dimethylamino or ethylmethylamino Y represents a reactive ethyl or methyl ester respectively, and, if the anion of the resultant quaternary ammonium salt is not the same as that of the required salt, converting the resultant quaternary ammonium salt into the corresponding required salt by direct metathesis or through the corresponding hydroxide or embonate.

2. A process as claimed in claim 1 wherein hexamethylene-1:6-bis-(dimethylamine) is quaternated with ethyl bromide, chloride, iodide or sulphate.

7

3. A process as claimed in claim 1 in which an aqueous solution of a quaternary ammonium salt formed by the reaction of a compound of the formula given in claim 1 and a compound Y as defined in claim 1 is treated with a water-soluble embonate, the embonate thus precipitated is collected and a hot aqueous solution thereof is treated with tartaric acid and the embonic acid thus precipitated removed to give a solution of the bitartrate containing the required cation.

4. A process as claime in any one of the preceding claims when carried out substantially as described in the foregoing Examples.

5. Hexamethylene - 1:6 - bis - (dimethylethylammonium) salts when prepared by the process hereinbefore particularly described and ascertained.

Dated this 3rd day of December, 1951.

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Witness.—L. Trollope.

8

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